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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,625	08/24/2006	Antonello Pietrangelo	LABM-11	2297

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EXAMINER	
MAIER, LEIGH C	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
01/11/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,625	PIETRANGELO ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 16-36* is/are rejected.

7)☒ Claim(s) *12-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 16, 2009 has been entered.

Any rejection or objection not expressly repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-6 and 22-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999).

Tamura teaches the preparation of a conjugate of a therapeutic agent for the treatment joint diseases, such as arthritis, and hyaluronic acid (HA) or a salt thereof. The agent may be attached to HA at a hydroxyl group by activating a carboxyl group in the therapeutic agent to prepare an ester linkage. See abstract and paragraphs [0001]; [0057]-[0059]; and [0072]-[0077]. The reference further teaches the preparation of a pharmaceutical composition of the conjugate. The pharmaceutical composition may be prepared in a form suitable for local or parenteral administration. See paragraph [0086]. The reference is silent regarding the concentration and pH of said composition. The reference teaches the general use of these therapeutic agents, see paragraph [0034], but is silent regarding rhein or a derivative thereof.

Smith teaches that diacerhein (diacetylated rhein) has utility for the treatment of osteoarthritis. See abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the product of Tamura by the use of rhein, or a derivative, such as diacerhein, as the therapeutic agent to be conjugated to HA and administer it for the treatment of osteoarthritis with a reasonable expectation of success because this agent is known to be useful for this therapeutic method. In the absence of unexpected results, it would be within the scope of the artisan to optimize the level of esterification of HA in preparing the conjugate through routine experimentation. It would be further within the scope of the artisan to optimize the concentration of the conjugate in a composition, as well as the pH of the composition for this utility through routine experimentation. In administering the conjugate for the treatment of the inflammatory disease, osteoarthritis, the method of "tissue repair" would also be accomplished. With respect to the claims to medical "products" and "devices" the examiner finds no requirements for these products not provided by a pharmaceutical composition, per se.

Applicant's arguments filed October 16, 2009 have been fully considered but they are not persuasive.

Applicant argues that Tamura fails to provide motivation to prepare a conjugate with *any* therapeutic agent having activity in joint diseases with a reasonable expectation of success. The examiner maintains that that is exactly what Tamura teaches as set forth in previous prosecution. Applicant's position appears to be that in order to prepare any conjugate, one of ordinary skill must prepare *every possible* conjugate. This is not the case. The artisan need only select any joint active compound. As far as the determining the appropriate way to form a conjugate, there are

limited active sites on HA and limited active sites on rhein. It would be within the scope of the artisan to select among these. As discussed previously given the structure of diacetylrhein, the free carboxyl moiety would present itself to one of ordinary skill as the obvious active group to be activated to form a conjugate with HA. This type of linkage is clearly suggested by Tamura.

Applicant further notes purported unexpected advantages. The first of these being the improved activity of the conjugate for inhibition of IL-1 induced MMP expression compared to unconjugated rhein. Applicant cites Example 7 and Figure 5. (It appears that Applicant intends Example 6 rather than 7, as Example 7 is drawn to a synthetic method.) Applicant argues that this is unexpected. However, in the disclosure, Applicant admits that "hyaluronic acid and thein have been reported to have beneficial effects in osteoarthritis due to their ability to inhibit the activity of metalloproteinases (MMP) involved in cartilage catabolism." See paragraph [0104]. The examiner agrees that this activity was known in the art at the time the invention was made. See, for example, Moreland (Arthritis Res. Ther., 2002) at pp 58-59. Therefore, this combined effect could not be considered unexpected. As Applicant has admitted, the inherent anti-inflammatory properties of HA are what they are. This remains true, regardless of the fact that they were not recognized by Tamura.

Another purported unexpected result is the stability of the inventive conjugate. Again, as discussed previously, the disclosure reports the stability of the purified conjugate. However, there is no comparison with other HA conjugates or any explanation as to why this is unexpected. Applicant fails to present any evidence that this is indeed unexpected and significant.

Claims 1-11 and 20-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Perbellini et al (WO 2004/056877).

Tamura teaches as set forth above. The reference further teaches the purification of conjugates by various methods, including dialysis. See paragraph [0084].

Smith teaches as set forth above.

The references do not teach the preparation of a conjugate comprising reacting the acid chloride of rhein with hyaluronic acid.

Perbellini teaches the preparation of a conjugate comprising reacting hyaluronic acid with an acid chloride. See abstract; all of page 11; and page 12, lines 7 and 8.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the conjugate made obvious by the combination of Tamura and Smith by the process of reacting hyaluronic acid with rhein acid chloride. The artisan would reasonably expect success because this reaction sequence is taught by Perbellini. It would be further obvious to purify the product by dialysis because this is also suggested by the reference.

Claims 1-11 and 16-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Perbellini et al (WO 2004/056877) and Kuhla et al (US 4,788,187).

Tamura and Smith teach as set forth above.

Perbellini teaches as set forth above. The reference does not teach the preparation of said acid chloride using methylene chloride as the solvent or an inert atmosphere for the reaction.

However, these are typical reaction conditions known in the art. See, for example, Kuhla at example 2 (step 1) at col 20.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use any known synthetic organic technique, such as an acid chloride reactant for the esterification of HA, to prepare a conjugate of rhein, or derivative thereof, as set forth above with a reasonable expectation of success. In the absence of unexpected results, it would be within the scope of the artisan to select appropriate reaction conditions for the preparation of the acid chloride, based on those known in the art.

Allowable Subject Matter

Claims 12-15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. As discussed in previous Office actions, acylation using an acyl chloride reagent in nonpolar solvent is known. However, with respect to the derivatization of HA, per se, the art suggests either aqueous solution or polar organic solvent. Because of the highly hydrophilic nature of HA, the artisan would have no particular motivation to modify known procedures for derivatizing HA in a nonpolar solvent.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:30 to 4:00 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more. Information regarding the status of an application may be obtained from the Patent Application Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished application is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

/Leigh C. Maier/
Primary Examiner
Art Unit 1623